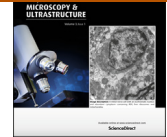




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## Original Article

# Bcl-2 may play a role in the progression of endometrial hyperplasia and early carcinogenesis, but not linked to further tumorigenesis<sup>☆</sup>



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## ABSTRACT

The role of Bcl-2 in initiation and progression of endometrial carcinoma is still with inconsistent results. The aim of this study is to determine the role of Bcl-2 in endometrial tumorigenesis. It is a retrospective cross sectional study. We used 100 endometrial paraffin embedded specimens for Bcl-2 oncoprotein immunohistochemical staining; 20 samples of normal endometrium, 40 specimens of endometrial hyperplasia (simple, complex and atypical) and 40 specimens of endometrioid adenocarcinoma. The results were statistically analyzed. There was a significant increase in Bcl-2 staining from normal through complex and atypical hyperplasia into well differentiated adenocarcinoma ( $P=0.002$ ,  $P=0.0008$  and  $P=0.0001$ , respectively). There was a significant difference between the staining of different types of endometrial hyperplasia; as it up streamed from the simple through the complex up to the atypical types ( $P<0.05$ ). Bcl-2 staining showed no significant correlation with the moderately, poorly differentiated and the different stages of adenocarcinoma ( $P=0.6$ ,  $P=0.29$  and  $P=0.1$  respectively).

These results might indicate a substantial role for Bcl-2 as one of the initiating drives for endometrial tumorigenesis, but not in further tumor progression.

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## 1. Introduction

Cancer of the uterine corpus is known to be the most common malignancy seen in the female pelvis, and it is twice as common as carcinoma of the ovary and the cervix. Endometrial carcinoma occurs during the reproductive and

menopausal years. The median age for adenocarcinoma of the uterine corpus is 61 years with the largest number of patients noted between 50 and 59 years. Multiple risk factors for endometrial carcinoma have been identified including; obesity, hypertension, diabetes mellitus, nulliparity, late menopause and positive family history [1–3].

In Egypt, uterine cancer is one of the most common gynecological malignancies. It showed the highest urban–rural incidence rate ratio, it also showed the highest urban incidence among the oldest age group (70+ age category) and in developed districts [4].

Apoptosis or programmed cell death is a well known fundamental feature that provides an efficient mechanism

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for eliminating cells, thus keeping cell numbers at constant levels in different organs. The B cell leukemia, lymphoma-2 gene (Bcl-2) was the first gene identified that inhibits apoptosis in many cell systems. This gene was first detected in follicular and diffuse lymphomas, but the finding of Bcl-2 expression in various epithelial tissues, such as breast, cervix and ovary suggested a possible role for development of some epithelial neoplasms [5–9].

Bcl-2 family proteins are known to play a crucial role in the regulation of the cell proliferation, as Bcl-2/BAX ratio keeps the proliferation balance of the endometrial cells. However, the definite role of this family in initiation, differentiation and invasiveness has not been well understood [10].

Cyclical variation in Bcl-2 expression in normal endometrial glandular epithelium has been suggested [10]. As Bcl-2 gene might increase the proliferative activity of the glandular endometrium [11], it might eventually lead to the development of endometrial hyperplasia and possibly neoplasia. The apoptotic mechanism has been shown to take place due to change in the expression of the gene family controlling the apoptosis [12–16].

Recently anti-Bcl-2 targeted therapy has been used in several tumors such as leukemia, small cell carcinoma of the lung, ovarian and breast cancers; thus the study of Bcl-2 expression in one of the most common gynecological diseases as endometrial hyperplasia and carcinoma becomes increasingly attractive [17].

Several studies investigated the Bcl-2 expression in normal and hyperplastic endometria as well as endometrial adenocarcinoma; with inconsistent results. Some authors showed increased Bcl-2 expression in endometrial carcinoma especially in low grade endometrioid type [10,18], while others showed decreased expression in endometrial carcinoma [19–22].

The aim of the present study was to investigate and compare the expression of the Bcl-2 oncoprotein in normal endometrium, and in cases of endometrial hyperplasia and endometrial adenocarcinoma searching for a possible role for Bcl-2 in the development of endometrial adenocarcinoma.

## 2. Materials and methods

### 2.1. Specimens and data collection

This retrospective study was conducted at Ain Shams University Specialized Hospital (ASUSH), Cairo, Egypt in the duration from March 2010 to March 2013.

The study included archival paraffin-embedded tissue specimens obtained from women following either endometrial curettage (D&C) or hysterectomy.

The criteria for the selection of the specimens were; normal endometrial specimens taken for endometrial dating in patients with infertility, endometrial hyperplasia (simple, complex and atypical) and endometrial adenocarcinoma (endometrioid type).

We tried to select the control group among women during the reproductive years of age as their endometrium is exposed to the normal hormonal effect that supposed to have a normal Bcl-2 expression. On the other hand, Bcl-2

is mainly expressed in proliferative endometrium under estrogenic stimulation [23], while in postmenopausal endometrium it is immunonegative or slightly positive to Bcl-2 [24].

We excluded specimens of patients with history of hormonal treatment, anti-estrogen treatment, chemotherapy or radiotherapy. Representative paraffin blocks and hematoxylin and eosin (H&E)-stained sections were retrieved from the pathology department at ASUSH, the rule of work in which is the consensus review of all the slides for confirmation of the diagnosis. The patients' files were reviewed to record the patients' age, weight, parity as well as the treatment protocol and the surgical FIGO staging in patients with cancer [25]. For statistical purposes; stages III and IV were grouped together.

The hospital Research & Ethical Committee approved the study. Institutional review board determined a waiver of patients' consent as data were collected and dealt with in an anonymous way.

### 2.2. Immunohistochemical staining

Formalin fixed, paraffin embedded tissue sections of 4 μm thickness were immunostained for Bcl-2 mouse monoclonal antibodies (clone 124; DAKO). The immunohistochemical technique was performed by applying the supersensitive avidin–biotin detection kit (Biogenex, CA, USA) and following the technique of Hsu and Raine [26]. For antigen retrieval, boiled water bath and sodium citrate buffer (pH 6.0) were used. To prevent the endogenous peroxidase cross reaction, 3% H<sub>2</sub>O<sub>2</sub> solution was used. The slides were incubated overnight with Bcl-2 antibodies at room temperature diluted 1:200. In parallel, positive controls (using normal human tonsil) and negative controls (by omitting the primary antibody) were performed to ensure correct staining procedure.

Bcl-2 oncoprotein expression was examined and further semi-quantitatively scored according to the intensity and extent of staining; (0) No immunostaining (1+) for weak positive staining and (2+) for strong positive staining [27].

The scoring was done by two independent pathologists who were unaware with the score results of each other.

### 2.3. Statistical analysis

Patients' characteristics were coded, entered, and processed by using SPSS (version 11). Description of quantitative variables was done using mean, standard deviation (SD), and range. One-way Anova test (analysis of variance) was used to test the difference between the mean values of the demographic data among the different groups. Fisher's exact test was used to compare the statistical difference of Bcl-2 expression scores between different groups in comparison to the normal endometrium. For statistical purposes; we added the number of the weakly and strongly positive cases together for each group. A *p*-value of 0.05 was considered the cut-off value for significance.

Our choice of the sample size was based on calculation by using STATA® version 11 programs, setting the type-1 error ( $\alpha$ ) at 0.05 and the power ( $1 - \beta$ ) at 0.8. The calculation was based upon references which claimed that

**Table 1**

Statistical correlation between the normal endometrium versus other groups with regard to immunohistochemical Bcl-2 staining.

Group (number of patients)	Negative Bcl-2 (%)	Positive Bcl-2		P
		Weak (1+) (%)	Strong (2+) (%)	
<b>Normal endometrium (20)</b>	16 (80%)	4 (20%)	0	
<b>Endometrial hyperplasia (40)</b>				
Simple (12)	10 (83%)	1 (8.5%)	1 (8.5%)	1
Complex (16)	4 (25%)	6 (34.5%)	6 (34.5%)	0.002*
Atypical (12)	2 (17%)	2 (17%)	8 (66%)	0.0008**
<b>Endometrial carcinoma (40)</b>				
Well differentiated (24)	4 (16.7%)	2 (8.3%)	18 (75%)	0.0001**
Moderately differentiated (10)	4 (40%)	2 (20%)	4 (40%)	0.06
Poorly differentiated (6)	3 (50%)	3 (50%)	0	0.29

\* P is significant.

\*\* P is highly significant.

Bcl-2 expression in proliferative endometrium in about 90–100%, while in endometrial hyperplasia it is 25–80% and 60–70% in endometrial carcinoma, so to find about 35% difference in expression of Bcl-2 between the control and either hyperplasia or carcinoma group, we had to have 19 control specimens and 35 specimens for each hyperplasia and carcinoma [18,19].

### 3. Results

We collected 109 specimens, nine of which had incomplete personal or surgical staging data, or had previous hormonal therapy. The remaining 100 specimens were; 20 normal endometrium (6 at proliferative phase, 7 at early secretory phase and 7 at late secretory phase), 40 endometrial hyperplasia (12 simple, 16 complex and 12 atypical), and 40 endometrioid endometrial carcinoma (24 well-differentiated [G1], 10 moderately [G2] and 6 poorly differentiated [G3]).

The demographic data of the patients revealed that age, parity and weight showed a significant statistical difference among the different groups ( $P < 0.0001$ ). The greatest values of age and weight were recorded among patients with endometrial adenocarcinoma.

Immunohistochemical staining of Bcl-2 in different specimens revealed weakly positive staining in only 4 normal endometrial biopsies (3 proliferative and 1 early secretory endometria). Staining of the endometrial hyperplasia specimens revealed up-streaming positivity from the simple through the complex ( $P = 0.002$ ) and up to the atypical type ( $P = 0.0008$ ) with significant statistical difference compared to the normal endometrium. The total positively stained specimens of the endometrial hyperplasia were 24 out of 40 specimens (60%); most of which showed strong positive staining (Table 1, Fig. 1).

Staining results of the different grades of endometrial carcinoma showed statistical significant difference between the normal endometrium and the well-differentiated adenocarcinoma ( $P = 0.0001$ ). There was a downstream positivity from the well differentiated type through the moderately and down to the poorly differentiated adenocarcinoma but the difference was statistically non-significant ( $P = 0.29$ ). The total positively stained specimens of endometrial carcinoma were 29 out of 40

specimens (73%); most of which were G1 and showed strong positive staining (Table 2, Fig. 1). There was no statistical significant correlation between the immunohistochemical staining of Bcl-2 and the different tumor stages ( $P = 0.1$ ) (Table 2).

### 4. Discussion

Several research studies investigated the correlation between Bcl-2 in endometrial hyperplasia and adenocarcinoma in comparison to the normal endometrium with inconsistent results regarding its role in endometrial carcinogenesis and differentiation [18–22].

This study showed a significant difference in Bcl-2 expression between the normal endometrium and both endometrial hyperplasia and carcinoma. There was a substantial increase in Bcl-2 expression in specimens of the complex and atypical hyperplasia as well as the well-differentiated endometrial adenocarcinoma. On contrary, the poorly differentiated endometrial adenocarcinoma showed decrease expression of Bcl-2.

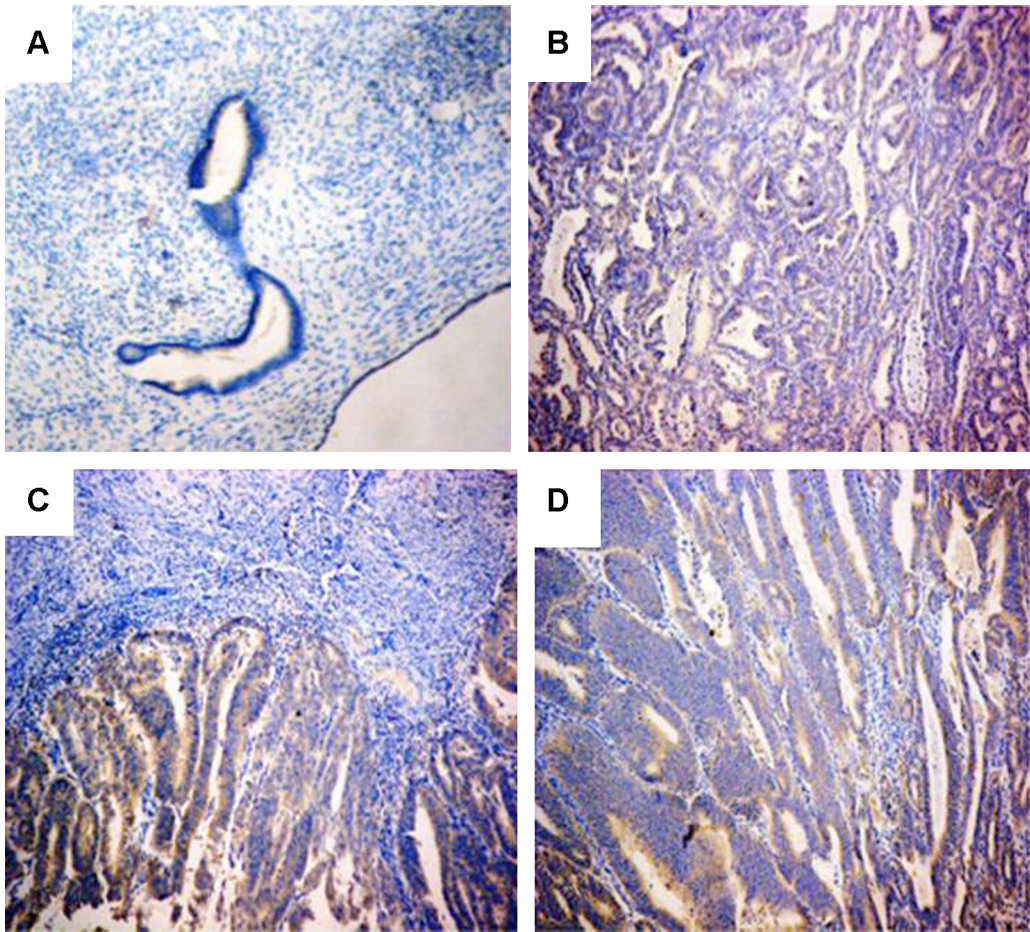
Staining of endometrial hyperplasia and the adenocarcinoma (G1) specimens revealed up-streaming positivity from the simple through the complex as well as the atypical type up to the well differentiated adenocarcinoma with significant statistical difference. However, this significant difference was lost when expression was compared in specimens with moderately and poorly differentiated adenocarcinoma. This might suggest that patients with complex and atypical hyperplasia are more likely to develop endometrial carcinoma than those with simple hyperplasia. Furthermore, it emphasized that Bcl-2 might act as an initiating impulse for carcinogenicity, afterwards, the aggressive biological behavior of the tumor would depend on factors other than Bcl-2.

Bcl-2 did not show an important role in endometrial cancer invasive capabilities, as there was no statistical correlation between the immunohistochemical expression of Bcl-2 and the different stages of the endometrial cancer.

One of the limitations of this study is its cross-sectional design; longitudinal follow-up was not done to confirm the study conclusion.

Strengths of the study were the fair size of the sample studied, the sample stratification; as it included all





**Fig. 1.** A; normal proliferative endometrial gland with focal weak Bcl-2 positivity. (Bcl-2  $\times$  200). B; complex endometrial hyperplasia, the endometrial glands are Bcl-2 positive, they are embedded in scanty endometrial stroma (Bcl-2  $\times$  100). C; well differentiated adenocarcinoma, D; moderately differentiated adenocarcinoma. Both show strong Bcl-2 staining positivity (Bcl-2  $\times$  100).

types of endometrial hyperplasia and all grades and stages of endometrial carcinoma. Furthermore, the semi-quantitative assessment for Bcl-2 staining into weak and strong could give us more information about the strength of association between Bcl-2 and the different types of endometrial pathology.

Our study revealed expression of Bcl-2 staining in normal endometrium (20%), endometrial hyperplasia (60%), and endometrial carcinoma (73%); the expression was more intense in the low grade compared to the high grade carcinoma. This was in agreement with Mourizikou et al. [10] who showed that Bcl-2 expression was more frequent

in low-grade carcinoma and none in the high grade. Marone et al. [18] stated that Bcl-2 was expressed in neoplastic endometrium more often than the normal counterpart.

There was no statistical significant correlation between Bcl-2 expression and the tumor stage which was in accordance with the results of Erkanli et al. [19] in which Bcl-2 staining results in endometrial carcinoma were nearly close to that of our study, they used biopsies of proliferative endometrium as a control; the results of BCL-2 staining in which were 100% positive and that was why they concluded that BCL-2 expression was less in endometrial carcinoma in comparison to the normal endometrium.

**Table 2**  
Statistical correlation between the different stages of the endometrial cancer and the normal endometrium regarding the immunohistochemical of Bcl-2 expression.

Stage = number of patients (%)	Number of patients with –ve Bcl-2 expression (%)	Number of patients with weak Bcl-2 expression (%)	Number of patients with strong Bcl-2 expression (%)	P
Normal endometrium (20)	16 (80%)	4 (20%)	0	0.2
I = 26 (65%)	5 (19.2%)	1 (3.8%)	20 (77%)	
II = 7 (17.5%)	4 (57%)	2 (28.5%)	1 (14.5%)	
III and IV = 7 (17.5%)	2 (28.5%)	5 (71.5%)	0	
Total = 40	11 (27.5%)	8 (20%)	21 (52.5%)	

This study showed different results with other studies that revealed that apoptosis increased when progressing from normal endometrium to hyperplasia and further to cancer. Decreased expression of Bcl-2 and increased rate of apoptosis in advanced malignancy might reflect the loss of cellular homeostasis and differentiation [20–22].

Progestins either orally administered or through levonorgestrel-releasing intrauterine system were used for conservative management of young patients with endometrial hyperplasia [28] and endometrial adenocarcinoma [29]. Also there was a decrease in glandular Bcl-2 expression in cases of endometrial hyperplasia after 3 months of treatment with levonorgestrel-releasing intrauterine system with a significant increase of apoptosis [30]. Consequently, Bcl-2 may be used as an independent prognostic marker; addition of Bcl-2 staining as a routine inexpensive histopathological marker may be useful to identify and follow up the small category of patients with atypical hyperplasia who may progress to endometrial adenocarcinoma and in need for the conservative medical treatment to retain their fertility. The presence of Bcl-2 expression in repeated D&C specimens from those patients might indicate the more probability of progression to adenocarcinoma and it can also predict the response to progestins therapy in those patients.

Longitudinal studies are needed to prove the role of Bcl-2 in the initiation of endometrial cancer; preferably by comparing the prognosis of two groups of patients with atypical hyperplasia and under conservative management; one with negative and the other with positive Bcl-2 expression.

In conclusion; Bcl-2 expression showed significant difference in the normal endometrium compared to both endometrial hyperplasia and well-differentiated endometrial adenocarcinoma. This might represent a key in understanding the initiation of endometrial neoplasia and serve as a possible prognostic marker for patients under conservative medical treatment for complex or atypical endometrial hyperplasia.

## Conflicts of interest

The authors received no financial support for their research, and they report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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